ORAL ARGUMENT NOT YET SCHEDULED

No. 24-5235

IN THE

United States Court of Appeals for the District of Columbia Circuit

NOVARTIS PHARMACEUTICALS CORPORATION,

Plaintiff-Appellant,

v.

XAVIER BECERRA, *et al.*,

Defendants-Appellees.

On Appeal from the United States District Court
for the District of Columbia, No. 24-cv-02234
Before Dabney L. Friedrich, J.

BRIEF FOR PLAINTIFF-APPELLANT

CATHERINE E. STETSON
SUSAN M. COOK
MARLAN GOLDEN
HOGAN LOVELLS US LLP
555 Thirteenth Street, N.W.
Washington, D.C. 20004
(202) 637-5491
cate.stetson@hoganlovells.com

Counsel for Novartis Pharmaceuticals Corporation

November 21, 2024

CERTIFICATE AS TO PARTIES, RULINGS, AND RELATED CASES

A. PARTIES AND AMICI

1. The following were parties in the District Court:

a. Plaintiff-Appellant: Novartis Pharmaceuticals Corporation.

b. Defendants-Appellees: Xavier Becerra, in his official capacity as the Secretary of Health and Human Services, and Robert M. Califf, in his official capacity as the Commissioner of the Food and Drug Administration.

c. Intervenor-Defendants-Appellees: MSN Pharmaceuticals Inc. and MSN Laboratories Private Ltd.

2. For purposes of Federal Rule of Appellate Procedure 26.1 and Circuit Rule 26.1, Novartis Pharmaceuticals Corporation certifies that Novartis Finance Corporation is its direct parent corporation, and that Novartis Pharmaceuticals Corporation is an indirect, wholly-owned subsidiary of Novartis AG.

B. RULINGS UNDER REVIEW

Novartis appeals the District Court's October 13, 2024 order denying Novartis's motion for summary judgment and granting Defendants' cross motions for summary judgment. JA___–__; *Novartis Pharms. Corp. v. Becerra*, No. 24-CV-02234 (DLF), 2024 WL 4492072 (D.D.C. Oct. 13, 2024) (Friedrich, J.).

C. RELATED CASES

The appeal docketed as *Novartis Pharmaceuticals Corporation v. Becerra* (D.C. Cir. 24-05186) is a related case under Circuit Rule 28(a)(1)(C). This Court dismissed the appeal as moot on October 31, 2024.

/s/ Catherine E. Stetson
Catherine E. Stetson

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GLOSSARY

ACE	Angiotensin-Converting Enzyme
ANDA	Abbreviated New Drug Application
APA	Administrative Procedure Act
ARB	Angiotensin II Receptor Blocker
FDA	Food and Drug Administration
FDCA	Food, Drug, and Cosmetic Act
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
LVEF	Left Ventricular Ejection Fraction
NDA	New Drug Application

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JURISDICTIONAL STATEMENT

The District Court had subject-matter jurisdiction under 28 U.S.C. § 1331. The District Court entered judgment on October 13, 2024. JA____ [Order]. Novartis timely appealed on October 14, 2024. JA____ [Notice of Appeal]. This Court has jurisdiction under 28 U.S.C. § 1291.

INTRODUCTION

FDA has a statutory and regulatory mandate to require that the labeling and active ingredients of a generic drug be the "same" as its reference listed drug. These sameness requirements play a critical public-health function: They ensure that generic drug products are just as safe and effective as their brand-name counterparts, protecting patients who rely on these therapies and innovator manufacturers—like Novartis—who have invested heavily in developing important new therapies. When FDA fails to enforce these statutory and regulatory requirements, the agency runs afoul of its governing statute and regulations. That is what has occurred here.

FDA's approval of an application by MSN Laboratories Private Ltd. seeking to market a purported generic version of Novartis's drug product ENTRESTO® (sacubitril/valsartan) violated the agency's governing statute and regulations regarding "sameness" in three ways.

First, FDA allowed MSN to omit from its labeling critical safety instructions directing health care providers to use a modified dosing regimen for certain vulnerable patient populations. The statute instructs that the labeling for generic drugs must be identical to that of the reference listed product. The regulations provide that omissions from the generic labeling are prohibited when they make the product less safe or effective. FDA's own assessment of the dosing regimen in ENTRESTO's labeling confirms that its omission from the generic's label undercuts

the generic product's safety and effectiveness. FDA's regulations accordingly forbid this dosage carve-out.

Second, FDA's regulations permit the agency to "omit" an indication in narrow circumstances. But FDA did not *omit* an approved indication for the MSN product; it *rewrote* the indication altogether, regressing to a previous ENTRESTO label and adding new language. Quite unlike ENTRESTO's labeling, which follows the current science and describes the indication for all adult patients with heart failure, the generic's labeling contains a strictly quantitative indication, indicating use only for patients with an ejection fraction measure within a particular range—a sharp discordance between these two "same" products, given that the generic product must be authorized on the basis of the same clinical and non-clinical data as the reference listed drug. FDA has failed to provide any reasoned analysis for this departure from ENTRESTO's non-quantitative indication.

Finally, FDA may approve only those generic drug products that are pharmaceutically equivalent to their reference listed drug. That equivalence requires that a generic share the "same" active ingredients as the listed drug. 21 U.S.C. § 355(j)(2)(A)(ii)(III). ENTRESTO's active ingredient is a *complex* of the anionic forms of sacubitril and valsartan; MSN's active ingredients are the separate *salts* sacubitril sodium and valsartan disodium. FDA thus impermissibly conditioned the

approval of MSN's generic on the safety and effectiveness finding for ENTRESTO—a drug product with a different active ingredient.

Each of these failures independently renders the agency's decision unlawful under the Administrative Procedure Act (APA) and invalidates the agency's approval of the MSN product. The District Court was wrong to conclude otherwise, and this Court should set aside the agency's unlawful action.

ISSUE PRESENTED FOR REVIEW

Whether FDA's denial of Novartis's citizen petitions and approval of MSN's Abbreviated New Drug Application referencing Novartis's product ENTRESTO violated the Administrative Procedure Act, where FDA left out critical safety instructions on the labeling for the generic product; FDA rewrote ENTRESTO's indication statement on the generic's labeling; and the generic does not have the same active ingredient as ENTRESTO.

PERTINENT STATUTES AND REGULATIONS

Pertinent statutes and regulations are reprinted in the Addendum.

STATEMENT OF THE CASE

A. Statutory and Regulatory Background

The Drug Approval Process

The Federal Food, Drug, and Cosmetic Act (FDCA) provides the statutory framework for FDA's regulatory oversight of drug products. To gain approval to

market a new, brand-name drug, a manufacturer submits a New Drug Application (NDA), demonstrating with scientific studies that the drug is safe and effective. 21 U.S.C. § 355(b)(1).

Generic drugs are approved through an Abbreviated New Drug Application (ANDA). 21 U.S.C. § 355(j). ANDAs generally do not include new clinical data. Instead, they rely on the same clinical and non-clinical data for the previously approved drug, known as the "reference listed drug," 21 U.S.C. § 355(j)(2)(A), and upon FDA's finding of safety and effectiveness for that reference-listed drug. An ANDA thus need not independently demonstrate safety or effectiveness; it must only establish that the generic product is "the same as" a reference listed drug already known to be safe and effective. *See id.* § 355(j)(2).

To make this showing of sameness, an ANDA must demonstrate that the proposed generic is "pharmaceutical[ly] equivalent" to the reference listed drug (that is, it contains the same active ingredient, in the same strength, dosage form, and route of administration); it has the same labeling and is labeled for the same conditions of use as the reference drug; and is "bioequivalent" to the reference drug (that is, it has the same rate and extent of absorption of the active ingredient(s) at the site of action). *See* 21 U.S.C. § 355(j)(2)(A).

An ANDA applicant seeking approval for a generic drug covered by a listed patent may challenge that patent by submitting a so-called "paragraph IV

certification," *see* 21 U.S.C. § 355(b)(2)(A)(iv), for each challenged patent timely listed in the FDA's publication *Approved Drug Products With Therapeutic Equivalence Evaluations*—more commonly known as the "Orange Book." Alternatively, for patents directed to a use of the reference drug, an ANDA applicant may submit a "section viii" statement indicating that the applicant does not seek approval for the use claimed by the patent. *See* 21 U.S.C. § 355(j)(2)(A)(viii).

The Same-Labeling Requirement

The FDCA generally requires an ANDA applicant to demonstrate that its proposed labeling is the same as the reference listed drug's labeling. 21 U.S.C. § 355(j)(2)(A). Absent a successful patent challenge, there are only two limited exceptions to this sameness principle: The ANDA labeling may differ from the labeling of the reference listed drug only if those differences are due to a suitability petition,[1] or because it is manufactured and distributed by different companies than the reference listed drug. 21 U.S.C. § 355(j)(2)(A)(v).

FDA has issued regulations addressing the statutory same-labeling requirement, "emphasiz[ing] that the exceptions to the requirement that a generic drug's labeling be the same as that of the listed drug are limited." FDA, *Abbreviated New Drug Application Regulations*, 54 Fed. Reg. 28,872, 28,884 (July 10, 1989). In

[1] A "suitability petition" is a petition to permit the filing of an ANDA for a drug that differs from the reference listed drug in certain respects not relevant in this case.

relevant part, FDA regulations provide that differences based on "different manufacturers" may reflect labeling differences due to marketing exclusivity or patent rights—but only so long as "such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use." 21 C.F.R. § 314.127(a)(7); *id.* § 314.94(a)(8)(iv). In those same regulations, the agency also took the position that labeling differences designed to avoid patent protection or regulatory exclusivity must only take the form of an ***omission*** in the labeling:

> Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers.
>
> Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or ***omission of an indication or other aspect of labeling protected by patent or accorded exclusivity*** under section 505(j)(5)(F) of the Federal Food, Drug, and Cosmetic Act.

21 C.F.R. § 314.94(a)(8)(iv) (emphasis added). This rule is driven by the agency's related position that if an ANDA applicant submits a section viii statement, it must omit from its labeling the use covered by the patent. FDA, *Application for FDA Approval to Market a New Drug*, 68 Fed. Reg. 36,676, 36,682 (Jun. 18, 2003) ("In

determining whether an ANDA applicant can 'carve out' the method of use, rather than certify to the listed patent, we will rely on the description of the approved use provided by the NDA holder or patent owner in the patent declaration and listed in the Orange Book.").

The agency's regulations go beyond the plain text of the statute. But under both the statute and regulations, an ANDA applicant must demonstrate that its proposed labeling is the same as the current labeling for the reference listed drug. Both talk about "the labeling approved for the listed drug"—which clearly refers to the current approved labeling. 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.127(a)(7); 21 C.F.R. § 314.94(a)(8)(iv).[2] Neither the statute nor the agency's regulations allow a generic to add information to the labeling or communicate in the labeling any conditions for use that are not the same as the approved conditions of use for the reference listed drug. 21 U.S.C. § 355(j)(2)(A)(i); *see also id.* § 355(j)(4)(B) (agency must deny approval if an ANDA fails to show that each of the proposed conditions of use for the generic has been approved for the reference listed drug).

[2] *See also* JA___ [AR 4579] (noting that in assessing labeling carve-outs, the agency must "start with the currently approved labeling" and that "earlier versions of the drug's labeling . . . have no relevance to this inquiry").

The Same Active Ingredient Requirement

The FDCA also requires that the generic have the same active ingredient as its reference listed drug. 21 U.S.C. § 355(j)(2)(A)(ii)(II) (requiring the generic applicant to "show that the active ingredients of the new drug are the same as those of the listed drug"). By regulation, FDA has defined "same as" for purposes of assessing pharmaceutical equivalence to mean, in relevant part, "identical in active ingredient(s)." 21 C.F.R. § 314.92(a)(1). And FDA's regulations clarify that an "identical active drug ingredient" is "*i.e.*, the same salt or ester of the same therapeutic moiety." 21 C.F.R. § 314.3(b) (definition of "pharmaceutical equivalents"). As the agency has noted in rulemaking:

> The agency interprets the requirement that the active ingredients in the proposed drug product be the same as those of the listed drug to mean that the active ingredients must be identical. For example, if the proposed drug product contained *a different salt or ester* of the active ingredient in the listed drug, the active ingredient in the proposed drug product would not be identical to the active ingredient in the listed drug, and could not, therefore, be approved in an ANDA. Active ingredient in this context means the active ingredient in the finished drug product prior to its administration.

54 Fed. Reg. at 28,881 (emphasis added). As the agency has further explained: "FDA has long regarded chemical structure as being fundamental to the identity of an active ingredient. Consequently, FDA regards *different salts and esters of the same therapeutic moiety as pharmaceutical alternatives* rather than pharmaceutical

equivalents." FDA Citizen Petition Response, Docket Nos. 00P-1550/CP1 and 01P-0428/CP1, at 28 (Feb. 15, 2022) (Consolidated CP Response) (emphasis added).

Accordingly, FDA has taken the position—for decades—that an active ingredient is defined by its chemical structure, including those portions of the molecule that cause the drug to be a salt. FDA, *Sameness Evaluations in an ANDA—Active Ingredients: Guidance for Industry* (Nov. 2022). FDA has confirmed:

> As part of the identity of an active ingredient, we generally consider the chemical form of an active ingredient to be the entire molecule, including those portions of the molecule that cause the drug to be an ester or salt.

Id. at 4.

B. Novartis's ENTRESTO

FDA approved ENTRESTO in July 2015. JA____–___ [AR 11–17]. ENTRESTO is currently approved to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. JA____ [AR 1470], ___ [ECF No. 1-1].[3] It also has an approved pediatric indication. JA___ [AR 1470].

ENTRESTO is comprised of two drug substances in a single chemical structure: sacubitril (which acts to block the action of neprilysin, thus preventing the

[3] In all relevant respects, the ENTRESTO labeling in the administrative record—approved by FDA in February 2021—is the same as the current ENTRESTO labeling that Novartis has submitted as an exhibit in this litigation. JA___–___ [AR 1469–1489]; JA___ [ECF No. 1-1]. That labeling, dated April 2024, reflects more recent revisions to the labeling that are not in dispute here.

breakdown of natriuretic peptides) and valsartan (which relaxes the blood vessels and lowers blood pressure). JA____ [AR 4252].

Heart failure is a complex clinical syndrome that affects millions of adults in the United States, and its prevalence is increasing. JA____,___ [AR 1446, AR 3725]. Studies estimate that it will eventually affect over 8 million adults by 2030. JA____,___ [AR 3725–26]. Heart failure patients are sometimes classified by their left ventricular ejection fraction (LVEF), a measure of heart pumping dysfunction. Ejection fraction is a measurement, expressed as a percentage, of how much blood the heart's left ventricle pumps out with each contraction. *See* American Heart Association, *Ejection Fraction Heart Failure Measurement* (last reviewed June 14, 2023), *available at* https://www.heart.org/en/health-topics/heart-failure/diagnosing-heart-failure/ejection-fraction-heart-failure-measurement.

When ENTRESTO was first approved in July 2015, it had an approved indication of reducing the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure and reduced ejection fraction, known by the shorthand acronym "HFrEF." JA__ [AR 19]. ENTRESTO's indication was based on the results of a clinical trial known as the PARADIGM-HF trial, which enrolled patients with heart failure with reduced ejection fraction of less than or equal to 40%. JA____,___ [AR 241–243].

In February 2021, FDA approved a supplement to ENTRESTO's NDA. AR 1466–1468. The supplement was premised on the results of a second clinical trial, known as the PARAGON-HF trial, which enrolled patients with chronic heart failure and left ventricular ejection fraction (LVEF) greater than or equal to 45%. JA____–___ [AR 3964–66]. Informed by the results of the PARAGON-HF trial, FDA re-evaluated its approach to the labeling of ENTRESTO, particularly with respect to reliance on ejection fraction as the basis for identifying the appropriate patient population. JA___ [AR 4013–14].

Based on the combined results of both trials, in February 2021 FDA proposed and approved a revised indication for ENTRESTO for the treatment of all patients with heart failure, and removed the use of ejection fraction in the indication as a basis for determining the appropriate patient population. JA____–___ [AR 1466–68]. FDA's revised indication includes not only chronic heart failure patients with reduced ejection fraction (that is, LVEF of less than or equal to 40%) but also those with LVEF greater than 40%, including those with preserved ejection fraction or "HFpEF"—which today is generally considered to be an ejection fraction of 50% or higher at diagnosis. JA____,___ [AR 1470, AR 1491] (revising Novartis's "proposed indication" and instead adopting "final indication").

ENTRESTO's current labeling thus shows that while benefits are most clear in patients with LVEF below normal, it is approved to treat all patients with chronic

heart failure. JA____,___ [AR 1470, 3980]. This move away from LVEF as a diagnostic criteria was coupled with a corresponding addition to the Indication and Usage section stating, "LVEF is a variable measure, so use clinical judgment in deciding whom to treat." JA____ [AR 1470]. Taken together, these statements make clear that the clinician may decide which patients may use ENTRESTO, regardless of LVEF status. JA____ [AR 1470].

This approach reflects a modern and more sophisticated understanding of heart failure, in which the medical community has transitioned away from using LVEF as a strict criterion for classifying heart failure. The FDA labeling decision for ENTRESTO under the PARAGON-HF supplement similarly reflects this transition. Over time, research has shown that certain hallmarks of heart failure—including structural heart disease, a history of commonly reported symptoms, and objective signs—may not be strictly correlated with LVEF, as was thought when ENTRESTO was originally approved. *See* JA____–___ [AR 3821–47]. In fact, LVEF can vary by patient age and sex and may even change over time within the same heart failure patient—suggesting that a single threshold for "normal" ejection fraction should be resisted. *See* JA____–___ [AR3759–67]. Certain heart failure patients with peculiar diagnostic profiles also may be in a transitory phase between HFrEF and HFpEF; for these patients, LVEF is less likely to predict the likelihood of clinical benefit. *See* Davide Margonato et al., *Heart Failure with Mid-range or*

Recovered Ejection Fraction: Differential Determinants of Transition, Cardiac Failure Rev. (2020).

As FDA itself has noted, ENTRESTO's current labeling reflects this new, more advanced consensus by moving away from LVEF as a strict diagnostic criterion, recognizing that the universe of heart failure patients cannot be neatly sorted using the old HFrEF/HFpEF taxonomy. JA____ [AR 3961]. As the agency acknowledges, "[N]o well-defined parameter has been established to demarcate HFpEF from HFrEF." JA____ [AR 3922]. Officials at FDA's Center for Drug Evaluation and Research (CDER) have noted that "[t]he relationship between LVEF and treatment effect" that the agency had observed "indicates a need to go beyond a dichotomous classification of HF based on a traditional LVEF cut-off." JA____–___ [AR 4638–41]. The officials thus noted that because ENTRESTO confers a clinical benefit for some heart failure patients with LVEF that falls below normal levels, but still sits above the "traditionally used cut-off of 40 or 45%" for HFrEF, FDA approved a new ENTRESTO label that does not turn on the HFrEF/HFpEF distinction, instead embracing other indicia of heart failure. JA____ [AR 4641].

Thus, ENTRESTO's labeling for adult patients now states: "ENTRESTO is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in *adult patients with chronic heart failure*. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal. LVEF is a

variable measure, so use clinical judgment in deciding whom to treat." JA____ [AR 1470] (emphasis added).

The TITRATION Study

Section 2.6 of the current ENTRESTO labeling describes a modified dosing regimen for patients not taking an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB)—two drugs that increase blood flow by relaxing and widening blood vessels—or who were previously taking low doses of these agents before starting on ENTRESTO.[4] JA___ [AR 1471].[5] Specifically, the labeling directs physicians and such patients to initiate treatment with a reduced dose of ENTRESTO and then to up-titrate to the target dose over a greater number of titration steps more slowly than is used for other patients. JA____ [AR 1471].

This modified dosing regimen is derived from a clinical study known as the TITRATION study. The TITRATION study was initiated because many reduced ejection fraction patients encountered by prescribers in clinical practice are not at target doses of ACE inhibitors and ARBs. JA____–___ [AR 3983–84]. TITRATION demonstrated that the dosing regimen in Section 2.6 of the ENTRESTO labeling resulted in fewer clinically relevant adverse events for this

[4] In other words, "ACE inhibitor or ARB-naïve patients."

[5] The modified dosing regimen appears at Section 2.6 of the current ENTRESTO labeling, JA___ [ECF No. 1-1], and at Section 2.5 of the ENTRESTO labeling that FDA included in the administrative record, JA___ [AR 1471].

patient group and allowed them to reach the efficacious target dose. JA____–___ [AR 3982–84]; JA____ [AR 3949]. The modified dosing regimen studied in TITRATION had important safety implications for patients.

Upon reviewing the TITRATION study, FDA concluded that "the benefits of [ENTRESTO] outweigh the risks. . . . We believe the key risks of hypotension, renal impairment, hyperkalemia, and angioedema can be adequately managed through clinical monitoring and dose titration," JA___ [AR 243], finding "[a] longer titration period with a starting dose of 50 mg bid may reduce the risk of hypotension, renal impairment and hyperkalemia in patients previously on a low dose of an [ACE inhibitor] or ARB," as well as patients who are not currently taking an ACE inhibitor or ARB. JA____ ___ [AR 301].[6]

The resulting modified dosing regimen is included in Section 2.6 of the ENTRESTO labeling, and states as follows:

> **2.6 Dose Adjustment for Patients Not Taking an ACE inhibitor or ARB or Previously Taking Low Doses of These Agents**
>
> In patients not currently taking an ACE inhibitor or an angiotensin II receptor blocker (ARB) and for patients previously taking low doses of these agents, start ENTRESTO at half the usually recommended starting dose. After initiation, increase the dose every 2 to 4 weeks in adults and every 2 weeks in pediatric patients to follow the recommended dose escalation thereafter [*see Dosage and Administration (2.2, 2.3)*].

[6] Hypotension is low blood pressure. Renal impairment is kidney impairment. Hyperkalemia refers to excess potassium in the blood.

> Note: Initiate pediatric patients weighing 40 to 50 kg who meet this criterion at 0.8 mg/kg twice daily using the oral suspension [*see Dosage and Administration (2.3, 2.4)*].

JA____ [AR 1471]. This important safety instruction has been in the FDA-approved labeling since ENTRESTO's original approval in 2015, JA____ [AR 19]; it both signals to patients and providers that the standard ENTRESTO dosing schedule could put ACE inhibitor or ARB-naïve patients at risk and provides critical instructions that allow for safe administration of the drug to such patients.

The labeling explicitly recognizes this modified dosing regimen must mitigate risks proactively for this patient population and directs physicians and patients to initiate treatment with a reduced dose of ENTRESTO and then to up-titrate to the target dose more slowly and over a greater number of titration steps than is used for other patients. JA____ [AR 1471]. FDA's assessment that "[ENTRESTO] has an acceptable safety profile in patients with HFrEF" and that "key toxicities of [ENTRESTO] can be managed through proper labeling" was based, in part, on findings from TITRATION and the inclusion of the regimen in the labeling. JA____ [AR 232].

Novartis is the owner of U.S. Patent No. 11,058,667 (the '667 Patent), which claims the modified dosing regimen for use in patients with heart failure with reduced ejection fraction. The '667 Patent issued on July 13, 2021 and expires on May 9, 2036. In addition, Novartis owns three patents that cover methods of using

sacubitril and valsartan in heart failure patients with preserved ejection fraction: U.S. Patent Nos. 9,517,226, 9,937,143, and 11,135,192. These patents, which have a presumption of validity (*see* 35 U.S.C. § 282(a)), are listed in FDA's *Orange Book*. Because of that patent protection, FDA cannot approve a generic product with labeling referencing the patented use until the relevant patent expires if a generic applicant does not challenge the patent or prevail in a litigation challenge to the patent. 21 U.S.C. § 355(j)(5)(B)(ii)-(iii).

C. The Same Active Ingredient Citizen Petition

In April 2019, Novartis submitted a citizen petition to FDA explaining that any generic version of ENTRESTO must have the same active ingredients in the same chemical form as ENTRESTO (the "Same Active Ingredient Citizen Petition"). JA____–___ [AR 2812–38]. In that petition, Novartis argued that ENTRESTO contains two active moieties, sacubitril and valsartan, in a single chemical structure and that this chemical structure must serve as the basis for establishing active ingredient sameness for any proposed generics. JA____–___ [AR 2817–31].

Novartis reminded FDA that its own framework for assessing sameness of active ingredients provides that an active ingredient of a drug product includes the specific salt, ester, or complex of the active moiety present in the drug product. JA____–___ [AR 2817–18] (citing 54 Fed. Reg. at 28,881). Novartis pointed out

that ENTRESTO consists of anions of sacubitril and valsartan together with sodium cations to form a single chemical structure. JA____ [AR 2819]. This structure is specifically called out in the FDA-approved labeling. JA____, ___–___ [AR 2820, AR 1476–77].

D. The Labeling Carve-Out Citizen Petition

In September 2022, Novartis submitted a citizen petition to FDA directed to the labeling of any potential generic products referencing ENTRESTO (the "Labeling Carve-Out Citizen Petition"). JA____–___ [AR 3959–90].

Novartis explained that it would be unlawful for FDA to revise the exclusivity- and patent-protected use in the approved indication by rewriting the indication to cover only patients with *reduced* ejection fraction. Novartis noted that an ANDA indication statement categorizing the patient population by reference to ejection fraction is inconsistent with the current ENTRESTO labeling, which reflects the agency's deliberate decision *not* to use ejection fraction as a strict diagnostic criterion to determine which patients may benefit from ENTRESTO. JA____–___ [AR 3971–80]. Novartis reminded the agency that generic applicants cannot reference discontinued labeling, such as the now-superseded ENTRESTO indication statement describing its use in patients with only "reduced ejection fraction." JA____–___ [AR 3978–80]; *see also supra* at 40–44.

The Labeling Carve-Out Citizen Petition raised another labeling carve-out issue. Novartis argued that the agency was prohibited from approving generic drug products whose labels contain the modified dosing regimen addressed in the TITRATION study and protected by the '667 Patent. JA___ [AR 3961]. Novartis also explained that FDA was prohibited from carving the modified dosing regimen out from generic labeling because doing so would render the purported generic product less safe and effective than ENTRESTO for the remaining conditions of use. JA___ [AR 3982].

Without the modified dosing regimen, patients with reduced ejection fraction who are ACE inhibitor or ARB-naïve or previously on low doses of these agents would be administered the generic product under the standard titration schedule in the labeling—including a higher starting dose and more rapid dosing regimen than that recommended for such patients. JA___ [AR 3982]. Novartis documented the harms that would arise if FDA approved a generic label that omitted the modified dosing regimen, explaining that it would fail to inform patients and providers of the safest option for administering the drug to heart failure patients with reduced ejection fraction who are ACE inhibitor or ARB-naïve. JA___ [AR 3982–3984].

E. Denial of the Citizen Petitions and Approval of MSN's Product

FDA denied Novartis's Same Active Ingredient Citizen Petition in May 2024. JA___–___ [AR 2783–2808]. Specifically, the agency rejected Novartis's argument

that the "same active ingredient" analysis should be based on the complex present in the finished dosage form of ENTRESTO.

To reach that conclusion, the agency asserted that ENTRESTO was comprised of two separate active ingredients, distinct salts *never previously identified by the agency* as present in the drug product: "sacubitril sodium" and "valsartan disodium." JA___–___ [AR 2800–01]. And it made this assertion even though FDA's Office of Pharmaceutical Quality (OPQ) had determined that the chemical nature of ENTRESTO is a complex, not a salt as FDA defines that term. JA___[AR58].

The agency concluded that ANDA applicants should "demonstrate 'sameness' based on the identity of the individual active ingredients of ENTRESTO (i.e., sacubitril sodium and valsartan disodium)." JA___ [AR 2803]. FDA made no effort to explain why these two separate salts are mentioned nowhere in the record accompanying ENTRESTO's approval and why they are not included in the labeling of ENTRESTO. In fact, ENTRESTO's labeling specifically calls out the complex comprised, in part, of sacubitril and valsartan anions. JA___–___ [AR 1476–77].

In July 2024, FDA denied Novartis's Labeling Carve-Out Citizen Petition. JA___–____ [AR 3910–54]. FDA asserted that notwithstanding its regulation, it retains the authority to approve generic labeling that not only "omits" an approved indication of the reference drug but also *revises* an approved indication. JA___–___ [AR 3935–36]. FDA also maintained that it could lawfully approve generic labeling

that lacks the modified dosing regimen for vulnerable patients it had approved in ENTRESTO's labeling. JA___–___ [AR 3948–51]. The next day, FDA updated the *Orange Book* to reflect its approval of an ANDA submitted by MSN identifying ENTRESTO as the reference listed drug.

F. Novartis's Legal Challenge

Novartis challenged those final agency actions in the District Court days after MSN's ANDA approval, filing both a Complaint and a motion for a temporary restraining order and/or preliminary injunction. The court denied the motion for preliminary injunction, reaching only the irreparable harm factor. JA___ [ECF 23]. Novartis appealed to this Court and filed an emergency motion for a stay pending appeal. On August 19, this Court granted Novartis's motion and stayed FDA's approval of the MSN product. Order, *Novartis Pharms. Corp v. Becerra*, No. 24-5186 (D.C. Cir.). Meantime, in separate patent appeals, the Federal Circuit granted and continued injunctions against MSN's commercial marketing on August 14 and 22.

Meanwhile, litigation continued in the District Court as the parties briefed cross-motions for summary judgment on an expedited basis. On October 13, the District Court granted the federal- and intervenor-defendants' cross-motions for summary judgment and denied Novartis's motion. The court ruled that FDA could delete ENTRESTO's modified dosing regimen from MSN's labeling, and that FDA

could accomplish a labeling omission through a labeling rewrite. The court also concluded that the two products had the same "active ingredients," blessing the agency's late-breaking re-naming of ENTRESTO's active ingredient. JA___ [ECF 68 at 14].

Novartis appealed. This Court subsequently lifted its stay in the preliminary-injunction appeal and dismissed the interlocutory action as moot on October 31.

SUMMARY OF ARGUMENT

I. FDA acted unlawfully by excluding part of ENTRESTO's dosing regimen from the MSN product's labeling. The FDCA requires that the labeling proposed for a generic be the same as the labeling approved for the reference listed drug. 21 U.S.C. § 355(j)(2)(A)(v). A generic drug product may include a labeling carve-out to address statutory marketing exclusivity or patent rights, so long as "such differences do not render the proposed drug *less safe or effective* than the listed drug for all remaining, nonprotected conditions of use." 21 C.F.R. § 314.127(a)(7) (emphasis added); *id.* § 314.94(a)(8)(iv). Yet the FDA-approved labeling for the MSN product does exactly that. The MSN generic's label omits mention of a modified dosing regimen derived from the results of a study demonstrating that the modified regimen results in fewer clinically relevant adverse events for ACE inhibitor or ARB-naïve patients (rendering it safer) and allows a greater proportion of these patients to reach the efficacious target dose (rendering it more effective).

FDA asserts that the dosage carve-out is permissible because the modified regimen might not be "the safest and best-tolerated option" for all patients, and because TITRATION's results do not show that the regimen was necessary for ENTRESTO's approval. That is not the standard. The standard is whether the generic's labeling renders the product *less* safe or effective than the listed drug—not whether the generic's labeling renders the drug product *un*safe or *in*effective, or whether the omitted material was critical to the reference-listed drug's approval. The agency violated the FDCA and its own regulations in ignoring the proper regulatory standard and approving the MSN product's labeling.

II. FDA further acted unlawfully with respect to the MSN product's labeling by rewriting the approved indication. It violated the FDCA, its own regulations, and the APA in reverting to a superseded indication and adding new language.

A. FDA's endorsement of the generic's labeling violates the plain text of the FDCA. Under the FDCA, the generic's labeling must match the *current* labeling for the reference listed drug. 21 U.S.C. § 355(j)(2)(A)(v). ENTRESTO's indication statement initially limited its use to patients with reduced ejection fraction. But it has evolved since its first FDA approval: clinical trial data now supports use of ENTRESTO for all patients with heart failure, regardless of their ejection fraction measure. Yet the labeling FDA approved for MSN's purported generic

impermissibly reverts to the original (and now superseded) indication for ENTRESTO by limiting the generic's use to patients with reduced ejection fraction. FDA violated the FDCA in endorsing this labeling flip-flop.

B. The agency's failed attempt to line-edit ENTRESTO's indication fares no better. The FDCA requires that the indications of the generic and listed drug are "the same," 21 U.S.C. § 355(j)(2)(A), and the agency's own regulations permit the "*omission* of an indication" to address a marketing exclusivity or patent right but not a rewriting of the listed product's current approved indication. 21 C.F.R. § 314.94(a)(8)(iv) (emphasis added). The word "omission" has a clear meaning: It is the act of leaving something out. By rephrasing the generic's indication to limit its use to patients with reduced ejection fraction, FDA was not merely leaving words out—it was *rewriting* the indication and *adding* words. Such a broad understanding of "omission" finds no support in the FDCA. The agency's novel take on its labeling carve-out power means the agency has created a condition of use for MSN's product that has never previously been approved for ENTRESTO—a result that runs roughshod over the law's same-labeling requirement.

C. FDA's complete rewrite of ENTRESTO's labeling is arbitrary and capricious, too. Because ENTRESTO's indication is non-quantitative—it is approved for all patients with heart failure, regardless of their ejection fraction measure—the current labeling recommends that physicians use their "clinical

judgment" in making prescription decisions. But the labeling of MSN's generic returns to a strictly quantitative indication, indicating use only for patients with reduced ejection fraction. FDA has provided no reasoned analysis to support this arbitrary departure from ENTRESTO's non-quantitative indication.

III. FDA acted unlawfully when it concluded that the MSN product satisfies the FDCA's active ingredient "sameness" test. FDA may approve only those generic drug products that are pharmaceutically equivalent to their reference listed drug; this equivalence requires that the generic and listed drugs share the "same" active ingredients. 21 U.S.C. § 355(j)(2)(A)(ii)(III). A generic's active ingredient is the same as the listed drug's if it is the same salt, ester, or complex of the active moiety. ENTRESTO and the MSN product contain different active ingredients. ENTRESTO is a complex of anionic forms of sacubitril and valsartan, while the generic's active ingredients are two salts, sacubitril sodium and valsartan disodium: salts of sacubitril and valsartan. Yet FDA concluded that the MSN product has the same active ingredients as ENTRESTO, belatedly identifying ENTRESTO's active ingredients as sacubitril sodium and valsartan disodium after previously recognizing that ENTRESTO is a complex formed from sacubitril and valsartan. That is unlawful.

STANDARD OF REVIEW

"When a district court reviews agency action under the APA," this Court "review[s] the district court's decision de novo." *Cigar Ass'n of Am. v. FDA*, 964 F.3d 56, 61 (D.C. Cir. 2020). Agency action should be set aside when it is "in excess of statutory jurisdiction, authority, or limitations, or short of statutory right" or "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A), (C).

ARGUMENT

I. FDA WRONGFULLY CARVED OUT CRITICAL SAFETY INSTRUCTIONS FROM THE GENERIC'S LABELING.

"A precept which lies at the foundation of the modern administrative state is that agencies must abide by their rules and regulations." *Reuters Ltd. v. FCC*, 781 F.2d 946, 947 (D.C. Cir. 1986). FDA violated that elementary principle.

The safety instructions FDA included in ENTRESTO's labeling outline a modified dosing regimen demonstrated to reduce the number of adverse events within a vulnerable patient group. FDA found the modified dosing regimen could "increase tolerability and reduce the risk of adverse events such as hypotension, hyperkalemia and renal impairment," and its clinical reviewers accordingly determined that "[w]e agree with the proposed titration strategy from a safety perspective." JA___ [AR 311]. These instructions have appeared in ENTRESTO's FDA-approved labeling from the beginning. JA____, __ [AR 19; ECF No. 1-1].

Yet when it approved MSN's product, FDA approved labeling *omitting* the modified dosing regimen. As FDA concedes, this shift is not based on any new data or information that might cast doubt on FDA's original conclusion. JA___. Instead, what underpins the agency's defense is a warped reading of the relevant regulatory standard.

The District Court blessed FDA's decision by extending a "high level of deference" to "FDA's scientific judgment." JA___ [ECF 68 at 18] (internal quotation marks and citations omitted). But FDA fumbled the law, not the science. FDA had previously concluded that ENTRESTO's modified dosing regimen may reduce the risk of adverse reactions in the relevant patient population, which is why it included the language on the ENTRESTO label in the first instance. JA___ [AR 311]. When explaining its approval of the carve-out for MSN's generic drug, however, the agency purported to reach a different conclusion, claiming it was "unknown" whether the dosing regimen is the "safest" and "best-tolerated" option. JA___ [AR 3949]. But the question is not whether the listed drug's labeling is the "safest and best-tolerated" option, but whether the generic's labeling renders it *less safe* than the listed drug. That is the case here, as omitting this regime will lead to a higher incidence of adverse events for some ACE or ARB-naïve patients.

The District Court also noted that FDA never stated that the dosing regimen was *necessary* to ENTRESTO's approval, and that prescribers can themselves

determine an initial appropriate dose even without the directive on the labeling. JA___ [ECF 68 at 20–21]. That laissez-faire approach reads FDA's safety and efficacy mandate out of its regulations; FDA must heed its regulatory obligation to ensure safety when approving dosage and administration instructions. And the court did not grapple with FDA's failure to explain why it found the modified dosing regimen appropriate "from a safety perspective" for ENTRESTO, JA___ [AR 311], but not backed by sufficiently robust results for the generic, JA___ [AR 3950].

Because the agency's misreading violates the regulation, its approval of MSN's product should be set aside.

A. FDA's Approval Of MSN's Product Reflects A Misapplication Of The Regulatory Standard.

When FDA approved ENTRESTO for use in treating adults living with heart failure, the agency concluded Novartis's product satisfied the core requirements for NDA approval: The drug is both safe and effective for its intended use. 21 U.S.C. § 355(d). Certain particularly vulnerable heart failure patients, however, face an elevated risk of experiencing adverse events when they are first prescribed ENTRESTO. To reduce the likelihood that these patients will suffer an adverse event, FDA included within ENTRESTO's labeling a modified dosing regimen—ensuring the drug remains safe for its intended use.

When FDA approved the MSN product, it relied on the same findings of safety and efficacy that supported the agency's approval of ENTRESTO—including the TITRATION study that had prompted FDA to include the modified dosing regimen in ENTRESTO's labeling. But because the agency was asked to carve out that modified dosing regimen from the generic's labeling, FDA was obliged to determine whether its omission would render the drug "*less safe*" than its reference product that includes those very instructions. 21 C.F.R. §§ 314.127(a)(7), 314.94(a)(8)(iv) (emphasis added).

The agency did not make that finding. FDA instead concluded that it was "unknown" whether the modified dosing information represents "the safest and best-tolerated option for such patients," JA___ [AR 3949], such that *removing* the information was acceptable because it was "not necessary to retain . . . in the labeling for generic sacubitril and valsartan tablets." JA___ [AR 3951]

But that is not the yardstick FDA must use to measure the safety of a generic product. Before granting ANDA approval, FDA must conclude that a proposed omission from the product's labeling "do[es] not render the proposed drug product *less safe* or effective than the listed drug for all remaining, nonprotected conditions of use." 21 C.F.R. § 314.127(a)(7); (emphasis added); *id.* § 314.94(a)(8)(iv). FDA's approval of the MSN product did not follow this regulatory standard.

The consequences of this agency error are manifold. The launch of MSN's product, stripped of its modified dosing regimen for a vulnerable subpopulation, will cause widespread confusion and mistaken attribution of adverse events to ENTRESTO across the patient population. Consider this scenario: A heart failure patient within the vulnerable subpopulation to which Section 2.6 is directed—someone who requires ENTRESTO's life-sustaining treatment but nevertheless faces an elevated risk of adverse events if she takes the normal dose—is prescribed sacubitril/valsartan by her physician. Because generic labeling must match that of its reference product, the physician consults MSN's labeling, and seeing no modified dosing regimen, prescribes the standard dosage. JA___ (Miller Decl. ¶¶ 21, 39–40). The patient then takes the medication as the generic labeling instructs: at the standard dosage. Soon she suffers an adverse event. There is harm to the patient, who has suffered needlessly and may now not be able to complete her treatment. And there is harm to Novartis, as all involved predictably assume that the company and its innovator product's labeling are to blame—a sad irony given that the ENTRESTO labeling would have plainly instructed that the patient should be started on a lower dosage and slowly up-titrated over time.

B. FDA Cannot Defend Its Omission Of The Modified Dosing Regimen.

The Government's primary response to this sort of preventable consequence is that there are other safety instructions in the MSN product's labeling. JA___ [AR

3950]. As FDA acknowledges, however, these are post-hoc instructions that provide guidance on "how to mitigate the risk of adverse reactions" once they occur. JA____ [AR 3950]. But at that point, the damage—to Novartis, but much more importantly to the patient—has already been done. It is entirely backwards from both a regulatory and ethical standpoint to argue that it is acceptable to allow a patient to suffer an adverse event that could have been avoided with the proper labeling because the remaining language tells the doctor how to treat that adverse event once it has occurs. That defense contradicts the agency's original rationale for modifying the dosing regimen, FDA's regulations, and judicial precedent.

1. The Record

ENTRESTO's approved labeling contains two types of safety instructions: Section 2's modified dosing regimen, which is designed to prevent adverse reactions in a vulnerable subpopulation of patients, and the instructions in Section 5, which direct providers on the course of treatment *after* a patient has suffered an adverse side effect. Those bookended safety instructions on the ENTRESTO label serve two different purposes. FDA included the modified dosing instructions in ENTRESTO's labeling because the modified dosing regimen is a "before" safety instruction, meant to prevent adverse events from happening in the first place; that is why the clinical reviewers "agree[d] with the proposed titration strategy from a safety perspective."

JA___ [AR 70]. The remaining safety instructions are concerned with the "after"; they direct providers' response to adverse events after they have occurred.

Front-end preventive instructions are not the same as back-end mitigation measures, which FDA understood when it decided both were necessary to ENTRESTO's safe use. And FDA further underscored the necessity of the dosing regimen for ACE inhibitor or ARB-naïve patients when it framed the instructions in mandatory terms, directing the provider to "start ENTRESTO at half the usually recommended starting dose. After initiation, increase the dose every 2 to 4 weeks in adults and every 2 weeks in pediatric patients to follow the recommended dose escalation thereafter *[see Dosage and Administration (2.2, 2.3)]*." JA___ [AR 1471].

2. FDA's Regulations

In addition to FDA's specific determination that the modified dosing regimen is a mandatory aspect of ENTRESTO's labeling, the agency is bound by the requirement that "[d]osing regimens must not be implied or suggested in other sections of the labeling if not included in this section." 21 C.F.R. § 201.57(c)(3)(ii); *see also id.* § 201.57(c)(2)(i)(D) (a reference to "any modification of dosage" in the indications and usage section of the labeling "must include" "a concise description of the information *with reference to the more detailed information in the 'Dosage and Administration' section*") (emphasis added). The Section 5 statements are, by

their terms, "Warnings and Precautions"—not dosing information. JA___ [AR 1470]. FDA's own regulations provide that the agency cannot shoehorn these important modified dosing instructions into other subsections of the label.

Even if that approach were permissible under FDA's regulations, the closest Section 5 of the labeling comes to hinting that this vulnerable population needs a modified dosing regimen is its warning that the product "must not be used in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy *[see Contraindications (4)*]." JA___, ___ [ECF No. 1-1, MSN Labeling]. There is a world of difference between this Section 5 precautionary statement against any use of ENTRESTO whatsoever and Section 2.6's specific safety instruction, which prescribes a particularized dosing regimen for patients who have *never been on* an ACE inhibitor or ARB, or who have previously taken only low doses of those agents.

3. Precedent

The Government's about-face also cannot be squared with case law outlining the agency's obligations under both the FDCA and the APA.

The agency's position is far afield from the standard regulatory paradigm: A product's safety is assessed based on the conditions of use that the label identifies, not on unspoken assumptions about what physicians might know, or what they are likely to do. *See Sigma-Tau Pharms., Inc. v. Schwetz*, 288 F.3d 141, 148 (4th Cir.

2001) (FDA properly "declined to examine other evidence besides the proposed labeling in approving the generic drugs at issue"); *see also Riegel v. Medtronic, Inc.*, 552 U.S. 312, 318 (2008) (same for device approvals, where "FDA evaluates safety and effectiveness under the conditions of use set forth on the label").

With the label FDA approved for the generic, healthcare providers are left without critical guidance when they treat ACE inhibitor or ARB-naïve patients who receive a generic product lacking ENTRESTO's dosing instructions. And yet the Government is eager to make the agency's regulatory duty the doctor's problem, suggesting that healthcare providers may fill the void by advising at-risk patients on an ad-hoc basis. JA___ [AR 3950] ("The Agency believes that health care practitioners are in the best position to determine an appropriate initial dose of Entresto using the information contained in Entresto's labeling, including section 5."). But that information in Section 5 does not provide the same instructions, and it is not addressed to the specific patient population of ACE inhibitor or ARB-naïve patients. If busy practitioners were required to research appropriate dosing instructions on their own, it is difficult to see what function FDA-approved dosing instructions would serve. Labeling instructions in fact serve a vital, and obvious, patient-safety function, which is why FDA approved the modified dosing regimen's inclusion in ENTRESTO's labeling in the first place. JA___–___ [AR 456–457].

The agency's decision to jettison that approach when it came to the MSN labeling is unlawful.

Speculation about how a drug is likely to be used based on information *not* present in generic labeling also is not the sort of agency determination that merits weight from the Court, particularly when it runs counter to the evidence the agency found sufficient to support safety instructions for the reference listed drug. JA___, ___ [AR 311, AR 456–457]. If FDA wants to treat ENTRESTO and the MSN product differently, it must " 'support th[e] disparate treatment with a reasoned explanation' " that is present "on the record before the Court." *Lilliputian Sys., Inc. v. Pipeline & Hazardous Materials Safety Admin.*, 741 F.3d 1309, 1313 (D.C. Cir. 2014) (quoting *Burlington N. & Santa Fe Ry. Co. v. Surface Transp. Bd.*, 403 F.3d 771, 777 (D.C. Cir. 2005)).

In *Lilliputian Systems*, this Court found that an agency inadequately justified disparate treatment of similarly situated items by failing to explain its risk evaluations. *Id.* at 1313–14. The Pipeline and Hazardous Materials Safety Administration (PHMSA) prohibited flammable-gas fuel cell cartridges in checked airline baggage. *Id.* at 1313. Yet it allowed medicinal and toiletry items containing that same sort of flammable gas in checked baggage. *Id.* This Court held that differential treatment violated the APA because both contain the same kind of hazardous material and, as checked baggage, are packed, handled, and stowed in the

same manner. *Id.* Though the agency insisted it considered the "[c]umulative risk" of allowing both kinds of flammable-gas articles aboard, it said "nothing about *how* it evaluated the cumulative risk or *why* its evaluation led to the prohibition of one category of similarly situated articles and not the other." *Id.* That failure could not be squared with the APA's requirement of reasoned decision-making. *Id.* at 1314.

A similar pattern unfolded in *Clean Wisconsin v. Environmental Protection Agency*, 964 F.3d 1145 (D.C. Cir. 2020), where this Court found that EPA insufficiently explained its disparate treatment of similarly-situated areas and drew conflicting conclusions from the same data. *Id.* at 1163. After EPA promulgates a new or revised National Ambient Air Quality Standard, it must designate each "area" in the country as "attainment," "nonattainment," or "unclassifiable." *Id.* at 1153 (quotation omitted). In 2015, EPA revised the air quality standard, *id.* at 1154, and designated one Missouri county as nonattainment because of its contributions to area violations, *id.* at 1162, while designating a community in a neighboring county as attainment. This, despite the fact that both contained stationary sources emitting similar amounts of nitrous oxides. *Id.* The Court held that EPA violated the APA by treating these "genuinely similar counties dissimilarly." *Id.* (quotation omitted).

This Court also noted that EPA had unlawfully treated the underlying data inconsistently. "EPA present[ed] the same data in support of" both designations but reached different outcomes—without supplying a reasoned basis for doing so—and

yet the agency nevertheless "believed this unchanged data supports" both conclusions. *Id.* Because EPA was unable to explain why the data supported one conclusion for County A and yet the same dataset supported a different decision for neighboring County B, the Court had little trouble concluding the agency was clinging to "a belief that makes no sense given the agency's earlier emphasis on this very same data" to reach a different conclusion. *Id.*

FDA's defense of its labeling carve-out here is similarly deficient: FDA has said nothing to explain why its evaluation of the TITRATION study would lead it to conclude for ENTRESTO that the modified dosing regimen is appropriate "from a safety perspective" for inclusion on the label, JA___ [AR 311], and for a generic version of the same drug that the regimen is not backed by sufficiently robust results, JA [AR 3950]. Either the results are "not robust" enough to put the modified dosing regimen in the labeling of either product, or are they sufficiently robust to include it in both. JA___ [AR 3950].[7] The Government has not only failed to justify the discrepancy: It also has expressly disclaimed in this litigation that any new data or evidence backs up FDA's differential treatment:

> THE COURT: And is there something that's led FDA to say now that it couldn't in 2015 that including this language is superfluous and it's not doing any work, it's not -- it's not preventing people from having

[7] As the District Court observed at the summary-judgment hearing, "however or not robust that study was, [FDA] had some basis enough so that they included the language, and now they're not including it now." JA___.

> adverse effects any more than just simply telling physicians to use their clinical knowledge and experience and make these determinations?
>
> Is there anything you can point to in the record that explains why that's -- the Court can conclude that FDA had a basis to say it's not any less safe to omit this language?
>
> FDA COUNSEL: Your honor, I can say that the agency's decision that it was no less safe and effective was not based on any new developments in the understanding of these adverse events in the years subsequent to Entresto's original approval.
>
> Whether there is any -- whether any literature like that exists in the record, I'm not certain. I know that the agency didn't rely on it in its decision, to my knowledge.

JA____.

The agency tries to wrap its decision in deference by suggesting that "FDA has determined as a scientific matter that" other precautionary warnings in the MSN labeling "are sufficient." JA____ [AR 3951]. But this is an inquiry into the proper regulatory standard—not the propriety of safety instructions in the first instance. The regulation requires a showing that the omissions in the generic product's labeling do not render it less safe or effective. 21 C.F.R. § 314.127(a)(7); *id.* § 314.94(a)(8)(iv). Because the agency asked the wrong question, it reached the wrong result. Its disparate treatment of the study data, and its approval of the MSN product, accordingly violates the APA.

II. THE MSN PRODUCT DOES NOT HAVE THE SAME INDICATION AS ENTRESTO.

When FDA approves the labeling of a generic drug, it is not drafting on a blank slate. The agency must carry forward the current FDA-approved labeling for the reference product. Here, that is the 2021 labeling FDA approved for ENTRESTO, which reflects a new paradigm for treating heart failure in an expanded set of patients. JA__ [ECF No. 1-1].

Novartis had proposed for that labeling that ENTRESTO bear two indications in heart failure: one for reduced ejection fraction, and another for preserved ejection fraction. JA___ [AR 1491]. But FDA rejected Novartis's proposal, instead opting for a single indication statement. Reflecting the evolved understanding of how heart failure functions, FDA revised ENTRESTO's labeling to eliminate the previous reference to "reduced ejection fraction" and eschewed a quantitative measure of ejection fraction. JA___–___, ____ [AR 4012–13, AR 3944] (documenting shift from Novartis's "proposed indication" to FDA's approved "final indication"). ENTRESTO thus is approved for use in all heart failure patients.

When MSN submitted its ANDA referencing ENTRESTO, however, the agency confronted a problem: The generic applicant did not seek approval for the same expanded indication statement FDA had drafted and approved for ENTRESTO. But because ENTRESTO has one indication, FDA could not simply omit it from the generic's approved labeling. Instead, FDA crafted a Franken-label.

The MSN product's labeling states: "Sacubitril and valsartan tablets are indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure *and reduced ejection fraction*. Left ventricular ejection fraction (LVEF) is a variable measure, so use clinical judgment in deciding whom to treat." JA___ [MSN Labeling] (emphasis added).

The District Court acknowledged that "[t]he plain text" of the agency's regulations refers to the omission of an indication. JA____ [ECF 68 at 16]. Nevertheless, the court concluded that the plain text did not refer to "the omission of particular words from the indication statement." JA____ [ECF 68 at 16]. This is a distinction without a difference: The plain meaning of an omission of an indication is the omission of—the act of leaving out—words from an indication statement, not rewriting the label. Whether or not FDA's rewrite belongs to the shapeless category of "substantive omissions" or not, an omission cannot be achieved by addition. JA____ [ECF 68 at 16–17].

The agency's rewriting of the approved indication thus violates FDA's governing statute and its binding regulations, and is arbitrary and capricious.

A. FDA Violated The FDCA By Approving MSN Labeling That Mirrors Now-Superseded ENTRESTO Labeling.

Begin with the text of the statute. The FDCA requires that the labeling for an approved generic be the "same" as the labeling for the reference listed product. 21 U.S.C. § 355(j)(2)(A). There are only two limited statutory exceptions to this

principle: The ANDA labeling may differ from the labeling of the reference listed drug only if those differences are due to a suitability petition, which all agree is not relevant here, or the fact that the products are "produced or distributed by different manufacturers." 21 U.S.C. § 355(j)(2)(A)(v). By its plain text, the "different manufacturer" exception would permit differences in generic labeling to identify a different manufacturer, product name, or company address. For that reason alone, the agency's position that language may be added to the indication violates the plain language of its governing statute.

This Court has previously accepted the Government's argument that the "different manufacturer" exception can be read to embrace significant labeling differences beyond those the statutory text is best read to permit. In *Bristol-Myers Squibb Company v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996), the panel read the statute to "permit[] an ANDA to be approved for less than all of the indications for which the listed drug has been approved." *Id.* at 1500 (quoting H.R. Rep. No. 98-857(I) (1984), *reprinted in* 1984 U.S.C.C.A.N. 2654–55)). But that case was decided under the outdated *Chevron* framework, which has now been overturned. Despite acknowledging that "BMS rests its case squarely upon the first step in [*Chevron*]" and framing the issue as whether "the statute clearly precludes such approval," *id.* at 1499, the opinion is marked by the *Chevron*-era approach to statutory interpretation. *See id.* at 1495 ("we read the Food, Drug, and Cosmetic Act, as amended, in the

same way the Secretary does"); *see also id.* at 1500 ("the Secretary's interpretation of the Act finds unusually strong support in the legislative history"). While the Court endorsed the agency's reading in that case, it never declared that interpretation to be the *best* reading of the statute, post-*Loper Bright*. *Loper Bright Enters. v. Raimondo*, 144 S. Ct. 2244 (2024).

In any event, this Court in *Bristol-Myers Squibb* had no occasion to answer the question this case asks: whether FDA may rewrite an indication or other aspect of labeling protected by patent, rather than simply remove one of several indications from generic labeling. Under a plain reading of the statute, the answer is no. When approving an ANDA, the agency lacks the statutory authority to redline *within* the innovator drug's approved indication or other aspect of labeling rather than merely omit a separate indication, as the agency did in approving MSN's product.

The statutory text is framed in the present condition: Both the statute and FDA's implementing regulations require sameness to "the labeling approved for the listed drug." 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.127(a)(7); 21 C.F.R. § 314.94(a)(8)(iv). "Same as the labeling approved for the listed drug" does not permit comparison between a generic drug's new labeling and a reference drug's old labeling: The generic drug must be compared to what the reference listed drug's labeling says *now*. JA___ [AR 4579] (in assessing labeling carve-outs, the agency

must "start with the currently approved labeling" and "earlier versions of the drug's labeling . . . have no relevance to this inquiry").

The generic labeling blessed by the agency does not match ENTRESTO's. It reverts to the now-superseded indication for ENTRESTO by confining its use to the reduced ejection fraction population. JA___ (MSN Labeling). But it is 2024, not 2015. A generic may *omit* an indication; it cannot rewind the clock and resurrect portions of an indication that FDA has retired for the generic.

The District Court resisted the premise, crediting the Government's assurances that FDA in fact compared the generic's labeling to ENTRESTO's current labeling. JA___ [ECF 68 at 15]. Setting aside whether it is mere coincidence that the MSN product's labeling matches ENTRESTO's original, superseded labeling rather than the extant version, the agency has still trapped itself in a vise: If FDA compared the generic's labeling to ENTRESTO's current labeling *while also* impermissibly reverting back to language in ENTRESTO's original labeling, the agency violated its governing statute. That reversion is apparent on the face of the labeling, and FDA's action is unlawful.

B. FDA's Addition To The Generic Labeling Is Not An "Omission."

The generic labeling also is unlawful because it violates the statutory requirement that the indications be "the same," 21 U.S.C. § 355(j)(2)(A), and the agency's own regulations, which permit "*omission* of an indication" to address a

marketing exclusivity or patent right, but not a rewriting of the reference product's current approved indication. 21 C.F.R. § 314.94(a)(8)(iv) (emphasis added).

FDA's regulations allow the "omission of an indication or other aspect of labeling protected by patent" to address a marketing exclusivity or patent right. 21 C.F.R. § 314.94(a)(8)(iv). Those regulations do not grant the agency the authority to remake out of whole cloth an indication statement that does not match the reference product's. "Omission" does not mean "addition": Removing something is not the same as adding it. FDA cannot arrogate broader authority to itself without promulgating a new rule. *U.S. Int'l Trade Comm'n v. ASAT, Inc.*, 411 F.3d 245, 253 (D.C. Cir. 2005) ("[T]he Commission is bound by its regulations.").

And yet FDA, under the banner of labeling omissions, added to ENTRESTO's labeling in order to approve MSN's product. The Court need not look far to conclude that "omission" in this context should not be read to mean the same thing as revision. FDA's regulation provides that "[s]uch differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include": (1) "differences in expiration date, formulation, bioavailability, or pharmacokinetics"; (2) "labeling *revisions* made to comply with current FDA labeling guidelines or other guidance"; or (3) "*omission* of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the Federal Food, Drug, and Cosmetic Act." 21 C.F.R. § 314.94(a)(8)(iv) (emphases added).

If FDA's use of "omission" were interchangeable with "revisions," one would expect the rule to use "revisions" in both clauses. But it does not. In the District Court, the Government explained the scope of authority that the term "labeling revisions" confers on the agency: "For example, in 2006, FDA dramatically revised the formatting that was required to control the layout of a package insert for prescription drugs. And adhering to that new formatting required *adding, revising, changing, moving things around in all sorts of ways that you would never describe as an omission* of an aspect of labeling or omission of an indication." JA___ [SJ Hearing] (emphasis added). That is precisely Novartis's point: Because adding something would never be described as omitting it, FDA cannot achieve an omission from ENTRESTO's labeling by means of addition.

The agency's revision of the ENTRESTO indication creates another problem: It creates a condition of use for the MSN product that was not previously approved for ENTRESTO. *See* 21 U.S.C. § 355(j)(2)(A)(i) ("An abbreviated application for a new drug shall contain information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a . . . listed drug"). FDA has asserted that the MSN product's labeling carves out patients with *normal* ejection fraction by adding language limiting the indication statement only to patients with *reduced* ejection fraction. JA___ [AR___]. However, within the Indications and Usage section of

the labeling, MSN included (and FDA unlawfully approved) an instruction on *usage* that was included in the labeling for Entresto only when the product was approved for the broad heart failure indication. JA___ [AR___]. The MSN labeling states, immediately after the supposed limiting language, that measurement of ejection fraction is variable, so clinicians should use their clinical judgment in deciding whom to treat with the drug. JA___ [AR___]. But when that exact same limiting language appeared in the original (now superseded) indication statement for ENTRESTO, *there was no statement instructing physicians to use clinical judgment rather than rely on measurement of LVEF*. JA___ [AR___].

The marriage of these two statements by MSN—"use only in patients with reduced ejection fraction and measurement of ejection fraction is variable, so use clinical judgment in deciding whom to treat"—was not previously approved for the reference product. This type of complete reconfiguring of a product's labeling by a generic drug sponsor finds no basis in the FDCA or its implementing regulations.

The District Court concluded that although FDA's implementing regulation uses the term "omission," it nevertheless does not bar "the omission of particular words from the indication statement." JA ___[ECF No. 68 at 16]. This is a heavy gloss on the regulatory text: The plain meaning of an omission of an indication is the omission of—the act of leaving out—words from an indication statement. Importantly, the term "omission" has a clear meaning: It means to leave something

out.[8] Nowhere do FDA's regulations grant the agency authority to approve non-substantive omissions from labeling while prohibiting substantive omissions. This Court need not mark the boundaries of which omissions are substantive and which ones are not; it is enough to conclude that an omission cannot be achieved by addition. The District Court erred in upholding FDA's approval of the rewritten indication statement adding language to ENTRESTO's labeling.

C. FDA's Conduct Is Arbitrary And Capricious.

FDA's actions also are arbitrary and capricious. FDA entirely failed to grapple with the qualitative shift in the formulation of ENTRESTO's indication when rejecting Novartis's Labeling Carve-out citizen petition. *See* JA___, ____–___ [AR 1470, AR 3963–66]; *see also* JA___–___ [AR 3940–42].

As Novartis has explained, ENTRESTO's operative labeling shows that the drug is approved for the broad use to treat chronic heart failure, and is not limited to use in patient populations with specific, quantified ejection fraction metrics. JA__ [AR 1470]. That is why the current labeling recommends that physicians use their "clinical judgment" in making prescribing decisions. JA___ [AR 1470]. MSN's

[8] *See, e.g.*, OMISSION, Black's Law Dictionary (defining term as "a failure to do something"; "the act of leaving something out"; "the state of having been left out"; "something that is left out"); Merriam-Webster Dictionary (defining "omission" as "something left out"); Britannica Dictionary (defining "omission" as "the act of not including or doing something"); Cambridge Dictionary (defining "omit" as "to fail to include or do something").

labeling, by contrast, reverts to the strictly quantitative approach that FDA scientists rejected in favor of ENTRESTO's current labeling. JA___ [AR 3963–66]. Those changes, and the data upon which those changes were based, were approved by FDA as an accurate representation of ENTRESTO's appropriate treatment indication. The agency has given no coherent explanation for its decision to backtrack from the currently approved non-quantitative indication.

This arbitrariness is all the more troubling when situated in context. The exceptions to the same-labeling requirement are extremely narrow and limited, and the exceptions permitting a generic to add language to omit a protected use are even more circumscribed as a matter of FDA practice. For example, where FDA allows a change in a product's inactive ingredients, the generic labeling may be required to add standard warnings and precautions relating to that particular inactive ingredient. FDA has explained that sort of addition may "fit squarely within the [regulatory] exceptions for (1) formulation differences and (2) differences required to comply with the labeling guidelines in the FDA's Sulfite warning regulation." *See Zeneca, Inc. v. Shalala*, 213 F.3d 161, 169 (4th Cir. 2000).

FDA also has permitted generic labeling to add a statement communicating that certain geriatric use information had been omitted because it was protected by exclusivity, permitting this language to reconcile the geriatric labeling regulations (which separately require the addition of geriatric use information) with the same-

labeling requirements. FDA Citizen Petition Response (Oxandrin), Docket No. 2005P-0383 (Dec. 1, 2006). In that scenario, FDA has allowed a generic to include a statement that the information had been omitted because that statement was required and specified under another agency rule. 21 C.F.R. § 201.80(f)(10)(iv).

Here, however, FDA points to no like circumstance where additions to labeling have been permitted. The District Court cited an administrative decision, never challenged in court, where FDA merely combined two different subsets of a single patient population to arrive at a more concise indication statement. JA___ (citing Velcade petition response); *see also* JA___ [AR 3946–47]. ENTRESTO is not that case: There is no easily divisible patient population here. FDA's approval of new labeling for ENTRESTO reflected fundamentally changed circumstances: The agency's understanding of the approved patient population, as well as the relevance of LVEF as a diagnostic criterion, had evolved since the drug's original approval. JA___–___ [AR 3971–74].

In sum, MSN's addition of language to the generic labeling to attempt a carve-out of the protected use does not fall within any recognized exceptions to the same-labeling requirement. FDA's failure to give an adequate explanation for this change in position is arbitrary and capricious because it is not justified by a "reasoned analysis." *Ramaprakash v. Federal Aviation Admin.*, 346 F.3d 1121, 1124–25 (D.C. Cir. 2003) (citation omitted). That, in turn, "necessarily requires the agency to

acknowledge and provide an adequate explanation for its departure from established precedent." *See Dillmon v. National Transp. Safety Bd.*, 588 F.3d 1085, 1089–90 (D.C. Cir. 2009). Where, as here, an agency does not "come to grips with conflicting precedent," that failure "constitutes an inexcusable departure from the essential requirement of reasoned decision making." *Ramaprakash*, 346 F.3d at 1125 (citation and internal quotation marks omitted).

III. THE MSN PRODUCT DOES NOT HAVE THE SAME ACTIVE INGREDIENTS AS ENTRESTO.

ENTRESTO and MSN's product are not the "same drug" in another respect: They do not share the same active ingredients. ENTRESTO is a complex of the anionic forms of sacubitril and valsartan with sodium cations.[9] MSN's active ingredients are the separate salts sacubitril sodium and valsartan disodium.

The District Court, however, concluded that ENTRESTO and MSN's generic share the same active ingredients by deferring to FDA's late-breaking revelation that both drug products actually contain "sacubitril sodium" and "valsartan disodium." JA___ [ECF 68 at 22]. The court opined that FDA had "consistently" treated ENTRESTO as "a different solid state physical form of the same salts," JA___ [ECF 68 at 24], but the record reveals otherwise. FDA determined in 2015 that the

[9] Anions are negatively-charged atoms or molecules, and cations are a positively-charged atom or molecule. They may exist as free ions, or in a complex or co-crystal with various co-formers (without forming a salt), or they may form discrete salts.

chemical nature of ENTRESTO's active ingredient is both a complex and a co-crystal, specifically noting that it is *not* a salt. JA___ [AR 58]. In its Quality Review, FDA again stated that the chemical nature of the active ingredient is both a complex and a co-crystal but not a salt. JA___ [AR 810–811]. FDA thus never suggested that ENTRESTO is a different *physical* form of the same *salts*; it instead expressly stated that the *chemical* nature of ENTRESTO's active ingredient is not a salt. The District Court wrongly deferred to FDA's sameness determination.

A. Unlike MSN's Product, ENTRESTO's Active Ingredients Are Not Separate Sodium Salts Of Sacubitril And Valsartan.

FDA may approve only those generic drug products that are pharmaceutically equivalent to their reference listed drug. That equivalence requires that they share the "same" active ingredients as the listed drug. 21 U.S.C. § 355(j)(2)(A)(ii)(III). In its implementing regulations, FDA defines "[p]harmaceutical equivalents" to require "identical amounts of the identical active drug ingredient, i.e., *the same salt or ester of the same therapeutic moiety*[.]" 21 C.F.R. § 314.3(b) (emphases added). *See also* FDA, *Sameness Evaluations in an ANDA*, *supra* at 10 (in evaluating sameness of active ingredients, FDA considers the portions of a molecule that cause a drug to be a salt, ester, or, where it "is intended to furnish pharmacological activity," a complex). As the agency has noted in rulemaking:

> The agency interprets the requirement that the active ingredients in the proposed drug product be the same as those of the listed drug to mean

> that the active ingredients must be identical. For example, if the proposed drug product contained *a different salt or ester* of the active ingredient in the listed drug, the active ingredient in the proposed drug product would not be identical to the active ingredient in the listed drug, and could not, therefore, be approved in an ANDA. Active ingredient in this context means the active ingredient in the finished drug product prior to its administration.

FDA, *Abbreviated New Drug Application Regulations*, 54 Fed. Reg. 28,872, 28,881 (July 10, 1989) (emphases added).

Simply put, a generic of a reference drug that is approved as a salt must have the same salt. If the reference drug is *not* a salt, the generic cannot include a salt. Similarly, if the reference drug is a complex or co-crystal of two active ingredients, the generic must also include those same two active ingredients. A generic that *includes* separate salts is not the same as a complex or co-crystal that *excludes* those salts. When determining active ingredient sameness, FDA minds differences in chemical structure. These are matters of first principle, set down by the agency in rules that have been consistently applied in the generic drug approval system for years.

But not in this case. The official FDA-approved labeling of ENTRESTO states: "ENTRESTO contains a *complex* comprised of anionic forms of *sacubitril and valsartan*, sodium cations, and water molecules in the molar ratio of 1:1:3:2.5, respectively." JA___ [AR 1477] (emphasis added). If this complex contained two separate salts, sacubitril sodium and valsartan disodium, the labeling would state so.

But it does not. ENTRESTO's labeling does not mention sacubitril sodium or valsartan disodium, only anionic forms of sacubitril and valsartan. Conversely, the ANDA record shows that MSN uses sacubitril sodium and valsartan disodium in the manufacture of its product—two separate salts. JA___ [AR 1896]. To get around this problem, the agency now insists that the active ingredient sameness test be applied to these two salts—chemicals that are found in MSN's product, not ENTRESTO. JA___–___ [AR 2800–01].

Yet in the decade-plus regulatory history of ENTRESTO, FDA has never before identified the active ingredients as the sodium salts of sacubitril and valsartan. *E.g.*, JA___–___, ___–___ [AR 57–119, AR 801–934]. These two salts are not identified in the NDA, or in the ENTRESTO labeling, nor are they listed in the Orange Book. JA___–___, __–___, ___–___ [AR 57–119, AR 801–934, AR 1469–89]. They do not occur at any stage in the manufacture, distribution, or administration of ENTRESTO. JA___–___ [AR 801–934].

FDA now describes the complex as a co-crystal, and therefore a physical form, not a contiguous chemical structure. But the inquiry remains the same: FDA must look to the underlying chemical structure, and what the co-crystal is composed of.

ENTRESTO is not composed of sacubitril sodium and valsartan disodium. Its labeling states that "ENTRESTO contains a complex comprised of anionic forms of sacubitril and valsartan, sodium cations, and water molecules." JA___ [ECF 1-

1]. It plainly does not say, "a complex (or co-crystal) of *sacubitril sodium* and *valsartan disodium*." MSN's labeling depicts sacubitril sodium and valsartan disodium. ENTRESTO's does not. These two separate salts are nowhere mentioned in the record until the eleventh hour when faced with a need to re-engineer ENTRESTO to match MSN's ANDA. The simple answer is found in the NDA and the labeling: The active ingredients in ENTRESTO are sacubitril and valsartan anions in a non-salt complex.

B. FDA Agreed That ENTRESTO's Active Ingredients Are Not Separate Sodium Salts Of Sacubitril And Valsartan—Until Approving MSN's Product.

Lest there be any doubt, in evaluating ENTRESTO, FDA stated that it is a complex formed from two separate drug substances and identified those drug substances as sacubitril and valsartan. JA____ [AR 1242]. The agency proposed that the term "complex" be used in ENRESTO's labeling instead of "sodium salt complex" precisely to avoid the misunderstanding that ENTRESTO's active ingredient is a salt. JA____ AR 58. And FDA's own regulations discuss a complex as distinct from a salt. 21 C.F.R. § 314.3(b) (defining an active moiety to exclude the parts of the molecule that "cause the drug to be an ester, *salt* . . . , or *other noncovalent derivative* (such as a *complex*, chelate, or clathrate) of the molecule") (emphases added); *see also Actavis Elizabeth LLC v. U.S. Food & Drug Admin.*, 625

F.3d 760, 762 (D.C. Cir. 2010) (citing 21 CFR § 314.108(a) (Dec. 4, 2016) (emphases added)); FDA, *Sameness Evaluations in an ANDA*, *supra* at 10.

In approving MSN's ANDA and denying Novartis's citizen petition, FDA abruptly changed course. Rather than require MSN demonstrate that its product has the same active ingredient complex as ENTRESTO, FDA has in its petition response retroactively projected the active ingredients in MSN's product back onto ENTRESTO, belatedly identifying ENTRESTO's active ingredients as "sacubitril sodium" and "valsartan disodium." JA___ [AR 2784]. That is not how the agency listed ENTRESTO's active ingredients in the *Orange Book*, which lists the drug substances as "SACUBITRIL" and "VALSARTAN."[10] If FDA determined the active ingredients were separate sodium salts, they would be listed in the *Orange Book* as separate sodium salts. If the active ingredients were separate sodium salts, they would be listed in the *Orange Book* as separate sodium salts. ENTRESTO's labeling would not describe a complex of anions of sacubitril and valsartan. And the agency would not have gone out of its way to ensure that ENTRESTO's labeling avoided a mistaken suggestion that the active ingredient is a salt.

[10] FDA can—and is required to—list a drug in the *Orange Book* in its salt form when that is the approved chemical form of the drug substance. *See, e.g.*, FDA, *Naming of Drug Products Containing Salt Drug Substances: Guidance for Industry* at 6 (Jun. 2015), https://www.fda.gov/files/drugs/published/Naming-of-Drug-Products-Containing-Salt-Drug-Substances.pdf. Hundreds of drug products are listed in the *Orange Book* with active ingredients shown as sodium salts and disodium salts. *See, e.g.*, *Orange Book*, Prescription Drug List, 44th Annual Edition (2024).

In a twist of irony, ENTRESTO would itself now fail the test for active-ingredient sameness (based on separate sacubitril sodium and valsartan disodium) put forward by the agency in approving MSN's product. To meet the sameness test, the active ingredients of the two drug products must actually be the same. Here they are not.

CONCLUSION

For the foregoing reasons, the District Court's judgment should be reversed.

Respectfully submitted,

/s/ Catherine E. Stetson
CATHERINE E. STETSON
SUSAN M. COOK
MARLAN GOLDEN
HOGAN LOVELLS US LLP
555 Thirteenth Street, N.W.
Washington, D.C. 20004
(202) 637-5491
cate.stetson@hoganlovells.com

Counsel for Novartis Pharmaceuticals Corporation

November 21, 2024

CERTIFICATE OF COMPLIANCE

Pursuant to Fed. R. App. P. 32(g)(1), the undersigned hereby certifies that this brief complies with the type-volume limitation of Fed. R. App. P. 32(a)(7)(B)(i).

1. Exclusive of the exempted portions of the brief, as provided in Fed. R. App. P. 32(f), the brief contains 12,992 words.

2. The brief has been prepared in proportionally spaced typeface using Microsoft Word for Office 2010 in 14-point Times New Roman font. As permitted by Fed. R. App. P. 32(g)(1), the undersigned has relied upon the word count feature of this word processing system in preparing this certificate.

/s/ Catherine E. Stetson
Catherine E. Stetson

November 21, 2024

ADDENDUM

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21 U.S.C. § 355(j)(2)(A)

21 U.S.C. 355(j)(2)(A)

(j) Abbreviated new drug applications

(1) Any person may file with the Secretary an abbreviated application for the approval of a new drug.

(2)

(A) An abbreviated application for a new drug shall contain--

(i) information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a drug listed under paragraph (7) (hereinafter in this subsection referred to as a "listed drug").

21 C.F.R. § 201.57(c)(2) & (3)

§ 201.57 Specific requirements on content and format of labeling for human prescription drug and biological products described in § 201.56(b)(1).

* * *

(c) ***Full prescribing information.*** The full prescribing information must contain the information in the order required under paragraphs (c)(1) through (c)(18) of this section, together with the headings, subheadings, and identifying numbers required under § 201.56(d)(1), unless omitted under § 201.56(d)(4). If additional subheadings are used within a labeling section, they must be preceded by the identifying number assigned in accordance with § 201.56(d)(2).

* * *

(2) ***1 Indications and usage.*** This section must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition.

(i) This section must include the following information when the conditions listed are applicable:

(A) If the drug is used for an indication only in conjunction with a primary mode of therapy (e.g., diet, surgery, behavior changes, or some other drug), a statement that the drug is indicated as an adjunct to that mode of therapy.

(B) If evidence is available to support the safety and effectiveness of the drug or biological product only in selected subgroups of the larger population (e.g., patients with mild disease or patients in a special age group), or if the indication is approved based on a surrogate endpoint under § 314.510 or § 601.41 of this chapter, a succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits, with reference to the "Clinical Studies" section for a discussion of the available evidence.

(C) If specific tests are necessary for selection or monitoring of the patients who need the drug (e.g., microbe susceptibility tests), the identity of such tests.

(D) If information on limitations of use or uncertainty about anticipated clinical benefits is relevant to the recommended intervals between doses, to the appropriate duration of treatment when such treatment should be limited, or to any modification of dosage, a concise description of the information with reference to the more detailed information in the "Dosage and Administration" section.

(E) If safety considerations are such that the drug should be reserved for specific situations (e.g., cases refractory to other drugs), a statement of the information.

(F) If there are specific conditions that should be met before the drug is used on a long term basis (e.g., demonstration of responsiveness to the drug in a short term trial in a given patient), a statement of the conditions; or, if the indications for long term use are different from those for short term use, a statement of the specific indications for each use.

(ii) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective or that the therapeutic benefits of the product do not generally outweigh its risks, FDA may require that this section state that there is a lack of evidence that the drug is effective or safe for that use or condition.

(iii) Any statements comparing the safety or effectiveness of the drug with other agents for the same indication must, except for biological products, be supported by substantial evidence derived from adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(c) of this chapter. For biological products, such statements must be supported by substantial evidence.

(iv) For drug products other than biological products, all indications listed in this section must be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(c) of this chapter. Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section.

(v) For biological products, all indications listed in this section must be supported by substantial evidence of effectiveness. Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section.

(3) ***2 Dosage and administration.***

(i) This section must state the recommended dose and, as appropriate:

(A) The dosage range,

(B) An upper limit beyond which safety and effectiveness have not been established, or beyond which increasing the dose does not result in increasing effectiveness,

(C) Dosages for each indication and subpopulation,

(D) The intervals recommended between doses,

(E) The optimal method of titrating dosage,

(F) The usual duration of treatment when treatment duration should be limited,

(G) Dosing recommendations based on clinical pharmacologic data (e.g., clinically significant food effects),

(H) Modification of dosage needed because of drug interactions or in special patient populations (e.g., in children, in geriatric age groups, in groups defined by genetic characteristics, or in patients with renal or hepatic disease),

(I) Important considerations concerning compliance with the dosage regimen,

(J) Efficacious or toxic concentration ranges and therapeutic concentration windows of the drug or its metabolites, if established and clinically significant. Information on therapeutic drug concentration monitoring (TDM) must also be included in this section when TDM is necessary.

(ii) Dosing regimens must not be implied or suggested in other sections of the labeling if not included in this section.

(iii) Radiation dosimetry information must be stated for both the patient receiving a radioactive drug and the person administering it.

(iv) This section must also contain specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams of active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed (e.g., the rate of administration of parenteral drug in milligrams per minute; storage conditions for stability of the reconstituted drug, when important; essential information on drug incompatibilities if the drug is mixed in vitro with other drugs or diluents; and the following verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.")

21 C.F.R. § 314.127(a)(7)

§ 314.127 Refusal to approve an ANDA.

(a) FDA will refuse to approve an ANDA for a new drug under section 505(j) of the Federal Food, Drug, and Cosmetic Act for any of the following reasons, unless the requirement has been waived under § 314.99:

* * *

(7) Information submitted in the ANDA is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the ANDA except for changes required because of differences approved in a petition under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers or because aspects of the listed drug's labeling are protected by patent, or by exclusivity, and such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use.

21 C.F.R. 314.3(b)

§ 314.3 Definitions.

(b) The following definitions of terms apply to this part and part 320 of this chapter:

* * *

Active moiety is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

* * *

Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, *i.e.*, the same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

21 C.F.R. § 314.94(a)(8)(iv)

§ 314.94 Content and format of an ANDA.

(a) ***ANDAs.*** Except as provided in paragraph (b) of this section, the applicant must submit a complete archival copy of the abbreviated new drug application that includes the following:

* * *

(8) ***Labeling*** —

* * *

(iv) ***Comparison of approved and proposed labeling.*** A side-by-side comparison of the applicant's proposed labeling including, if applicable, any Medication Guide required under part 208 of this chapter with the approved labeling for the reference listed drug with all differences annotated and explained. Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the Federal Food, Drug, and Cosmetic Act.

CERTIFICATE OF SERVICE

I certify that on November 21, 2024, the foregoing was electronically filed through this Court's CM/ECF system, which will send a notice of filing to all registered users.

/s/ Catherine E. Stetson
Catherine E. Stetson